Remarks

Reconsideration of this Application is respectfully requested.

Claims 1-32, 44, 48 and 62-70 have been canceled without prejudice or disclaimer to the subject matter thereof. Upon entry of the foregoing amendments, claims 33-43, 45-47, 49-61, and 71-75 are pending in the application, with claims 33, 42, 46, 58 and 72 being the independent claims. Claim 72 is a new claim and support for this claim can be found, *inter alia*, at page 10, lines 8-26, page 11, lines 1-12, page 15, lines 1-19, page 22, line 22 through page 23, lines 1 and 2 and in the claims 1-33 of the application as it was originally filed. Support for new claim 73 may be found on page 28, line 29, through page 29, line 2. Support for new claim 74 may be found on page 19, line 19, through line 23, in the specification. Support for new claim 75 can be found on page 21, line 24, through page 22, line 4.

No new subject matter is added by way of these amendments. Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Election/Restriction

In the Office Action dated January 11, 2002 (PTO Prosecution File Wrapper Paper No. 4), the Examiner has required restriction under 35 U.S.C. § 121 to an invention defined by one of the following five groups of claims:

Group I: Claims 58-61, 32-41, and parts of claims 1-4, 28, 29, 42-48, 51-57 and 71 (drawn to nicotinamides, compounds of Formula III);

Group II: Claims 62-65, 20-23, and parts of claims 1-4, 42-48, 51-57 and 71 (drawn to pyrazine amides, compounds of Formula VI);

Group III: Claims 66-69, 15-19, and parts of claim 1, 2, 4, 42-48, 51-57 and 71 (drawn to benzamido pyridines, compounds of Formula VII);

Group IV: Claims 5-14, 24-27, 30, 31, 51, 52, 70 and parts of claims 1-4, 28, 29, 42-48, 51-57 and 71 (drawn to heterocyclic carboxamides of Formula V); and

Group V: Claims 49, 50, 72 and 73 (drawn to complex compositions).

Applicants confirm the election, without traverse, the invention defined by the Examiner as Group I, claims 58-61, 32-41, and parts of claims 1-4, 28, 29, 42-48, 51-57 and 71. Applicants reserve the right to file divisional applications directed to the non-elected inventions.

The Examiner is of the opinion that:

> Claims 1-4, 28, 29, 42-48, 51-57 and 71 are rejected on the grounds as being drawn to an improper Markush group *In re Harnisch* 206 USPQ 300. The claimed compositions and methods that employ them present a variable core. Formula (V) contains compounds drawn to the non-elected inventions, with Ar' other than 3-pyridyl.

(Office Action, page 5, lines 9-13).

Claims 1-32, 44, 48 and 62-70 have been canceled. The amended claims refer only to compounds of the elected invention. Therefore, Applicants respectfully submit that the Examiner's stated grounds for rejection have been accommodated and the rejection should be withdrawn.

Rejections Under 35 U.S.C. § 112, second paragraph

A. First Rejection (Claims 1-4, 28, 29 and 32-41)

Claims 1-4, 28, 29 and 32-41 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. (Office Action, page 5, lines 18-19). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that:

> The phrases "a disorder responsive to the induction of apoptosis" and "a mammal in need of such treatment" are indefinite. The claims provide for the use of the compounds of formula V, but the claims do not set forth any steps involved in determining how to identify what disorders or mammals are to be treated. It is unclear what diseases and treatments applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how to practice this use. Identifying which diseases applicants intend this claim to cover will involve extensive and potentially inconclusive clinical research. With out such clinical research to identify the patients and diseases applicants intend to treat, one skilled in the art cannot determine the metes and bounds of the claim. Hence, the claims are indefinite.

(Office Action, page 5, line 19 through page 6, line 11).

The test for indefiniteness is whether one skilled in the art would understand the bounds of the claims when read in light of the specification. If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more. The degree of precision necessary for adequate claims is a function of the nature of the subject matter. *Miles Lab., Inc. v. Shandon, Inc.*, 27 U.S.P.Q.2d 1123, 1126 (Fed. Cir. 1993) (citations omitted).

It is well known to those of ordinary skill in the art what disorders are responsive to the induction of apoptosis. See, e.g., O'Reilly, L. A., *et al. Inflamm. Res. 48*:5-21 (1999) cited by Applicants as document AT4. O'Reilly states "[a]poptosis has been recognized as

an important regulator of tissue development and cellular homeostasis and abnormalities in this process have been implicated as a cause or contributing factor in a broad range of human diseases, including autoimmunity." O'Reilly at 14. See, also, Orrenius, S., *J. Intern. Med. 237*:529-536 (1995) cited by Applicants as AS5. Orrenius states "[f]inally, it has also become increasingly clear that apoptosis plays an important role in a number of diseases, including autoimmune disease, neurodegenerative disease, cancer and HIV/AIDS." Orrenius at 532. Thus, one of ordinary skill in the art would be apprized of what diseases or disorders may be treated according to the present invention based on the level of knowledge in the art and the teachings of the invention.

Further, examples of particular diseases and its symptoms the invention is used to treat can be found in the specification, *inter alia*, at page 22, last two lines, through page 24 line 2. Additional diseases are disclosed in the specification at page 26, line 1 through page 29, line 2. Furthermore, methods of treatment are described, *inter alia*, at page 24, lines 3-15 and at page 29, line 24, through page 30, line 2. Finally, the specification describes the animals intended to be treated with the invention on page 30, lines 13-16.

In addition, claims 33-41 recite an active positive step on how to practice the invention. Independent method claim 33 recites "[a] method of treating a disorder responsive to the induction of apoptosis . . . comprising *administering* to a mammal in need of such treatment an effective amount of a compound of Formula III." It is clear how to practice the invention, namely, by *administering* an effective amount of a compound. Claims 34-41 depend from claim 33 and therefore recite the same active language.

Therefore, Applicants respectfully submit the Examiner has not established a *prima facie* case of indefiniteness under 35 U.S.C. § 112, second paragraph. Applicants respectfully request that the rejection be withdrawn.

B. Second Rejection

Claims 1-4, 28, 29, 32-38, 40, 42-48, 51-57, 58, 60 and 71 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. (Office Action, page 6, lines 12-13). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that:

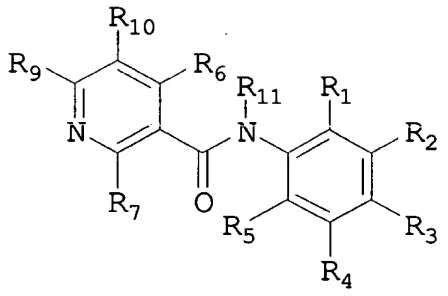
> The word "prodrug", which occurs in claims 1, 2, 33, 40, 42, 43, 46, 47, 58, and 60 is indefinite. The issue on second paragraph is whether the structures of the claimed compounds are clearly defined. Applicants' "prodrugs" are molecules whose structure lie outside the subject matter of claim 1, but upon metabolism in the body are converted to active compounds falling within the structural scope of claim 1. The claim describes the function intended but provides no specific structural guidance to what constitutes a "prodrug". Structural formulas, names, or both can accurately describe organic compounds, which are the subject matter of claim 1. Attempting to define means by function is not proper when the means can be clearly expressed in terms that are more precise.

(Office Action, page 6, line 15, through page 7, line 5).

Claims 1-32, 44, 48 and 62-70 have been canceled. The structures of "prodrugs" for the compounds of the invention are defined in the specification at page 21, line 24, through page 22, line 4.

The word "prodrug" is a term of art, well known to one of ordinary skill in the art. "Prodrugs" have been described in various publications, for example, by Leu, *et al.*, *J. Med. Chem. 42*:3623-3628 (1999) and by Greenwald, *et al.*, *J. Med. Chem. 42*:3657-3667 (1999). Copies of these references were submitted in an Information Disclosure Statement filed on June 25, 2001, as documents AT3 and AT2, respectively. Thus Applicants use of the word prodrug accords with the word's ordinary meaning.

With regard to claims 33-38, 40, 42-47, 51-57 and 58, the compounds are defined by Formula III, shown below.



(III)

The definitions of groups R_1-R_3 and R_5-R_{10} include hydroxy, hydroxyalkyl, amino, aminoalkyl, carboxy, alkoxycarbonyl and carbonylamido. The structures of the claimed "prodrugs," include esters, anhydrides, imines, carbamates, acetals and ketals of the groups R_1-R_3 and R_5-R_{10}. Claims 60 and 71 are directly or indirectly dependent upon independent claim 58.

For the reasons stated above, Applicants respectfully submit that the Examiner has not established a *prima facie* case for the rejection of claims 1-4, 28, 29, 32-38, 40, 42-48, 51-57, 58, 60 and 71 under 35 U.S.C. § 112, second paragraph. Applicants, therefore, respectfully submit that the above rejection has been overcome and should be withdrawn.

C. Third Rejection (Claims 1-4, 28, 29, 32-38, 40, 42-48, 53-57, 58, 60 and 71)

Claims 1-4, 28, 29, 32-38, 40, 42-48, 53-57, 58, 60 and 71 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 7, lines 6-7). Applicants respectfully traverse this rejection. The Examiner is of the opinion that: "[t]he phrases 'optionally substituted aryl', [']optionally substituted heteroaryl' 'Ar' is optionally substituted' etc, which occurs in claims 1, 2, 4, 28, 29, 32, 33, 34, 42-44, and 46-48, are indefinite. Optionally substituted by what?" (Office Action, page 7, lines 9-12).

Claims 1-4, 28, 29, 32, 44 and 48 have been canceled. In claim 33, R_{11} can be optionally substituted aryl or heteroaryl. The phrases "optionally substituted aryl" and "optionally substituted heteroaryl" groups are defined in the specification on page 19, lines 19-23. The term "Ar'" does not appear in any other pending claim. Thus, claims 33-38, 40, 42-43, 45-47, 53-57, 58, 60 and 71 are not indefinite. Applicants respectfully submit that this objection has been overcome and should be withdrawn.

Rejections Under 35 U.S.C. § 112, first paragraph

A. First Rejection (Claims 1-4, 28, 29 and 32-41)

Claims 1-4, 28, 29 and 32-41 have been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not allegedly described in the specification in such a way as to enable one skilled in the art to use the invention. (Office Action, page 7, lines 18-21). Applicants respectfully traverse this rejection. The Examiner is of the opinion that "[t]he how to use portion of the statute means that Applicants must teach the skilled practitioner, in this case a physician, how to treat the claimed disease. The physician clearly must know what disease and what symptoms she is to treat." (Office Action page 7, line 21, through page 8, line 3).

It is well known to those of ordinary skill in the art what disorders are responsive to the induction of apoptosis. See the discussion above on how one of ordinary skill in the art would know what diseases and symptoms to treat using the present invention.

Examples of specific diseases and its symptoms the invention is used to treat can be found in the specification, *inter alia*, at page 22, last two lines, through page 24, line 2. Additional diseases are disclosed in the specification on pages 26-28 and page 29, lines 1-2.

The treatment of these conditions is described in the specification, *inter alia*, at page 24, lines 3-15. Pharmaceutical compositions comprising the compounds of the invention are described in the specification, *inter alia*, at page 29, lines 3-18. The specification also describes the animals intended to be treated with the invention on page 30, lines 13-16. Finally, routes of administering the present invention are disclosed on page 30, lines 17-23.

Applicant's specification teaches a skilled practitioner how to practice the invention. Applicants respectfully submit that the rejection of claims 1-4, 28, 29 and 32-41 under 35 U.S.C. § 112, first paragraph has been overcome and the rejection should be withdrawn.

B. Second Rejection (Claims 1-4, 28, 29, 32-41, 42-48, 51-57, 58-61, and 71)

Claims 1-4, 28, 29, 32-41, 42-48, 51-57, 58-61, and 71 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. (Office Action, page 8, lines 4-8). Applicants respectfully traverse this rejection.

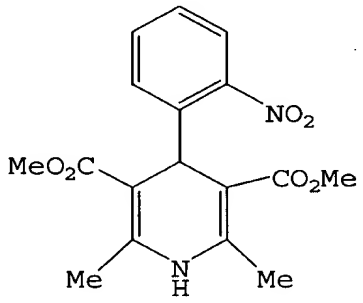
The Examiner is of the opinion that:

> As discussed by Testa (Burger's Medicinal Chemistry, 5ed, Chapter 6), the nitro aryl functional group is a toxophoric group. The table spanning both columns of page 177 lists eight suspect groups but only three, acetylene, aromatic nitro compounds, and thiols lack the qualifier "some" indicating these three are most problematic. The reason for the concerning regarding the toxicity of nitro aryl functional groups is provided by Low (Burger's Medicinal Chemistry, 4ed, Chapter 3) who states in the second paragraph on page 175, that such compounds are reduced enzymatically in the liver and produce highly carcinogenic hydroxylamines.
>
> Since Applicants' intended use of their compounds is as pharmaceutical agents, the likelihood of toxicity means the skilled clinician would not know how to use Applicants' compound for their intended purpose. The USPTO Board of Patent Appeals and Interferences held in *Ex*

> *parte Jovanovics* 211 USPQ 907 while Applicants "need not prove absolute safety or effectiveness", that "[t]he courts have held that, when a reasonable doubt exists, concerning the operability of a claimed invention, it is appropriate for an examiner to request a showing to resolve the doubt. *In re Ruskin*, 53 CCPA 872, 354 F. 2d 395, 148 USPQ 221; *In re Novak*, 49 CCPA 1283, 306 F. 2d 924, 134 USPQ 335. Since appellants' allegation that effective treatment of particular cancers in humans may be achieved with their new compounds is not entirely believable on its face, we believe that the examiner was justified in challenging the correctness of appellants' asserted utility."

(Office Action page 8, line 4 through page 9, line 10).

Drugs comprising the aromatic nitro functional group are not, as a general rule, toxic substances. There are at least twenty drugs on the U.S. market that comprise the aryl-nitro functional group. For example, Nifedipine, sold as PROCARDIA® by Pfizer and ADALAT® by Bayer, is an antihypertensive that contains the aryl-nitro functional group, and had a market value of approximately $1 billion in 1999. Its structure is shown below.



In light of the numerous drugs on the market that contain an aryl-nitro functional group, Applicants respectfully submit one of ordinary skill in the art would have no reason to believe the compounds of the invention, on their face, would be toxic and would not know how to practice the invention. Applicants, therefore, respectfully submit the Examiner has not established a *prima facie* case for doubting the reasonable operability of the invention. Applicants respectfully submit that the Examiner's rejection of claims 1-4, 28, 29, 32-41, 42-

48, 51-57, 58-61 and 71 under 35 U.S.C. § 112, first paragraph has been overcome and should be withdrawn.

C. Third Rejection (Claims 1-4, 28, 42-48, 51-57)

Claims 1-4, 28, 42-48 and 51-57 have been rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification does not reasonably provide enablement when Ar is aryl, generally, or heteroaryl. (Office Action, page 9, lines 11-13).

Claims 1-32, 44 and 48 have been canceled. Claims 42, 43, 46, 47, and 53-56 have been amended. Applicants respectfully submit that the Examiner's stated ground for rejection has been accommodated and the rejection should be withdrawn.

D. Fourth Rejection (Claims 42-48, 51 and 52)

1. First Argument

Claims 42-48, 51 and 52 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. (Office Action, page 10, lines 5-8). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that:

> Applicants are not enabled for "treating or preventing cancer" generally. There are two issues here. Firstly, [e]vidence involving a single compound and two types of cancer was not found sufficient to establish the enablement of claims directed to a method of treating seven types of cancer with members of a class of several compounds *In re Buting* 163 USPQ 689.
>
> To make clearer the lack of enablement for treatment of all cancer, extrinsic evidence is supplied by Draetta (Ann. Reports Med. Chem.), final

> sentence on page 246 "Although many still think about the need for a magic bullet as a cure for all cancers, our knowledge of the molecular mechanism underlying this disease make the prospect of developing such a universal cure very unlikely." Since no universal cure for cancer has been developed, it follows that there is no correlation between the assays relied upon by applicants and the ability to treat all cancers. Thus, those assays are not sufficient to enable such claims.
>
> The remarkable advances in chemotherapy have seen the development of specific compounds to treat specific types of cancer. The great diversity of diseases falling within the "tumor" category means that it is contrary to medical understanding that any agent (let alone a genus of thousands of compounds) could be generally effective against such diseases. The intractability of these disorders is clear evidence that the skill level in this art is low relative to the difficulty of the task.

(Office Action, page 10, line 8, through page 11, line 9). Applicants respectfully disagree with the Examiner's analysis and conclusions.

Applicants submit that Draetta (1996) does not reflect the great advances in the art. It is now known that cancer cells are, *inter alia*, generally characterized not only by a loss of cell cycle control but also by resistance to apoptosis. *See generally* Raymond W. Ruddon, *Biochemistry of Cancer, in* Holand-Frei Cancer Medicine, Chapter 2 (Robert C. Blast, Jr., *et al.* eds., 5th ed., B.C. Decker, 2000), a copy of which is attached herewith in a Second Supplemental Information Disclosure Statement and cited as AR12. Consequently, increasing the rate of apoptosis is recognized by those of ordinary skill in the art as an effective method for the treatment of a wide variety of cancers. *See, e.g.*, WO 00/04901, page 3, line 3, through page 5, line 6, a copy of which is submitted in a Second Supplemental Information Disclosure Statement and cited as AL4. Indeed, caspase activation is recognized, by those of ordinary skill in the art of cancer therapy, as a crucial requirement for the sensitivity of tumor cells toward drug-induced cell death. *See, e.g.*, Maret Los, *et al.*, "Cross-Resistance fo CD95- and Drug-Induced Apoptosis as a

Consequence of Deficient Activation of Caspases (ICE/Ced-3 Proteases)," *Blood 90*:3118-3129, 3128 (1997), a copy of which has previously been submitted as Document AS4 in an Information Disclosure Statement filed on June 25, 2001. Therefore, it is now recognized by those of ordinary skill in the art that agents that increase the rate of apoptosis are effective for the treatment of a wide variety of cancers.

For the reasons stated above, Applicants respectfully submit that the evidence submitted herewith is effective to rubut a *prima facie* case for non-enablement of claims 42-48, 51 and 52, under 35 U.S.C. § 112, first paragraph, and that the rejection should be withdrawn.

2. Second Argument

The Examiner further states:

> Secondly, Applicants are not enabled for preventing any disease. The only established prophylactics are vaccines not the nicotinamide analogs such as present here. Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of respiratory diseases generally. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished. *In re Ferens,* 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in the art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006. The Examiner suggests deletion of the word "prevention".

(Office Action, page 11, line 10 through page 12, line 2). Claims 42-48, 51 and 52 have been amended by removing the word "prevention." Applicants respectfully submit the Examiner's grounds for rejection have been accommodated and the rejection should be withdrawn.

E. Fifth rejection (Claim 53)

Claim 53 has been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to make and/or use the invention. (Office Action, page 12, lines 3-6). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that:

> The treatment of "autoimmune diseases" generally would be unprecedented feat. For a compound or genus to be effective against "autoimmune diseases" generally is contrary to medical science. The "autoimmune diseases" are a process that can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There are hundreds of such diseases, which have fundamentally different mechanisms and different underlying causes. There are both chronic and acute "autoimmune diseases", most of which lack satisfactory treatment. The intractability of these disorders is clear evidence that the skill level in this art is low relative to the difficulty of the task. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2d 1001, 1006.

(Office Action, page 12, line 6 through page 13, line 2). Applicants respectfully disagree.

Applicants respectfully submit that the Examiner has failed to recognize the great strides in understanding autoimmune diseases. As disclosed in the specification on page 26, lines 7-31, defective apoptosis can lead to autoimmune disorders, for example, autoimmune lymphoproliferative syndrome (ALPS). It has been reported in O'Reilly, *et al. Inflamm. Res.* *48*:5-21 (1999) that a treatment strategy for such diseases is to turn on apoptosis in an lymphocytes that are causing the autoimmune disease. This reference was submitted as

document AT4 in the Information Disclosure Statement filed on June 25, 2001. The specification in Examples 71-75, page 55, line 12, through page 61, line 18, discloses the use of the compounds of the invention in activating apoptosis in different cell lines. One of ordinary skill in the art, therefore, would know to use the compounds of the invention in the treatment of autoimmune diseases that are effected by apoptosis and the induction of the caspase cascade. The burden is not on the Applicant to prove that all molecules of the invention treat all autoimmune diseases.

Applicants submit that the evidence submitted herewith is effective to rebut a *prima facie* case under 35 U.S.C. § 112, first paragraph. Therefore, Applicants respectfully submit that the rejection of claim 53, under 35 U.S.C. § 112, first paragraph, has been overcome and should be withdrawn.

F. Sixth rejection (Claim 56)

Claim 56 was rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to make and/or use the invention. (Office Action, page 13, lines 3-6). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that:

> The scope of "skin disease" cannot be deemed enabled. The term "skin disease" covers a broad array of different disorders that have different modes of action and different origins. The term would embrace such unrelated disorders as sun burn, acne, and melanoma. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens,* 163 USPQ 609.

(Office Action, page 13, lines 6-11). Applicants respectfully disagree.

As disclosed in the specification, on page 27, lines 25-31 and page 28, lines 1-7, the induction of apoptosis in T cells could be the main mechanism by which certain treatments resolve psoriasis skin lesions, as reported in Ozawa, *et al.*, *J. Exp. Med. 189*, 711-718 (1999). This reference was included in an Information Disclosure Statement as document AT5, filed on June 25, 2001. The specification in Examples 71-75, pages 55-61, discloses the use of the compounds of the invention in activating apoptosis in different cell lines. Thus, one of ordinary skill in the art would be able to use the compounds of the invention to induce apoptosis in the treatment of psoriasis or other skin diseases that are effected by apoptosis and the induction of the caspase cascade. The burden is not on the Applicant to prove that all molecules of the invention treat all skin diseases.

Applicants submit that the evidence submitted is effective to rebut a *prima facie* case under 35 U.S.C. § 112, first paragraph. Applicants respectfully submit that the rejection of claim 56 under 35 U.S.C. § 112, first paragraph, has been overcome and should be withdrawn.

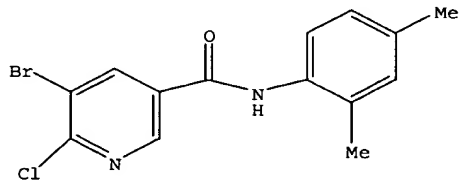
Rejections Under 35 U.S.C. § 102

A. First rejection (Claim 58)

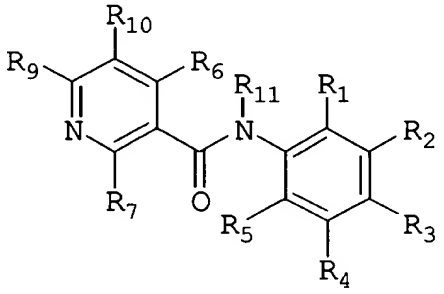
Claim 58 has been rejected under 35 U.S.C. § 102(b) as being anticipated by Setliff (*Proc. Arkansas Acad. Sci.*) (Office Action, page 14, lines 1-2). Applicants respectfully traverse this rejection. The Examiner is of the opinion that: "[t]he compound shown below

fits Formula III with $R_1 = R_3$ = methyl, $R_2 = R_4 = R_5 = R_6 = R_7 = R_{11}$ = hydrogen, R_9 = chlorine, and R_{10} = bromine." (Office Action, page 14, lines 2-3). Applicants respectfully disagree.

Setliff discloses 5-bromo-6-chloro-N-(2,4-dimethylphenyl)-3-pyridinecarboxamide:



In contrast to the disclosure of Setliff, the compounds of the present invention are defined by the structure shown below.



(III)

The compound 5-bromo-6-chloro-N-(2,4-dimethylphenyl)-3-pyridinecarboxamide of Setliff has a methyl group in the position corresponding to R_1 and R_3 in the compounds of the present invention. In contrast to the compound disclosed in Setliff, both R_1 and R_3 cannot be alkyl in the compounds of the present invention. Therefore, Setliff does not anticipate claim 58. Applicants respectfully submit that the rejection has been overcome and should be withdrawn.

B. Second rejection (Claim 58 and 71)

Claims 58 and 71 were rejected under 35 U.S.C. § 102(b) as being anticipated by Yagihara ('385 patent). (Office Action, page 14, lines 6-7). Applicants respectfully traverse this rejection. The Examiner is of the opinion that: "[t]here are two compounds in this reference which anticipated Applicants compound and composition claims. The compound shown below fits Formula III with $R_1 = R_5$ = ethyl, R_3 = fluorine, $R_2 = R_4 = R_{11}$ = hydrogen, R_6 = chlorine, $R_7 = R_9$ = methyl, and R_{10} = isobutyl." (Office Action, page 14, lines 7-10). Applicants respectfully disagree.

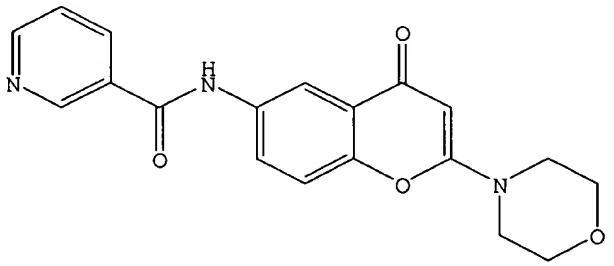
All compounds of Yagihara contain a halogen group in the position corresponding to R_6 in the present invention. In contrast, R_6 cannot be halogen in the compounds of the present invention. Therefore, Yagihara does not anticipate claims 58 and 71. Applicants respectfully submit that the rejection has been overcome and should be withdrawn.

C. Third rejection (Claim 1-4, 28, 29, 32, 42-48, 53, 54, 56 and 57)

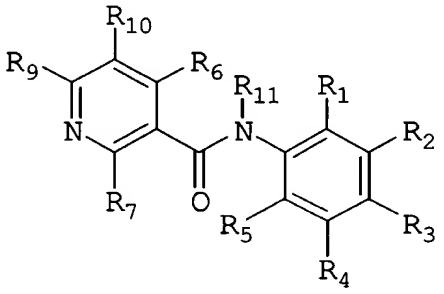
Claim 1-4, 28, 29, 32, 42-48, 53, 54, 56 and 57 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Gammill ('075 patent). (Office Action, page 15, lines 1-2). Applicants respectfully traverse this rejection. The Examiner is of the opinion that: "[c]ompound 16 of the reference anticipated Applicant's use claims and fits formula (V) with Ar'=3-pyridyl and Ar = 2-(4-morpholinyl)-4H-benzopyran-4-0n-6-yl. The compound is found in lines 54-55, column 20. Activity against cancer, arthritis, and psoriasis is disclosed

in lines 11-24, column 16." (Office Action, page 15, lines 2-6). Applicants respectfully disagree.

Gammill discloses, 6-(3-pyridinecarboxamide)-2-(4-morpholinyl)-4H-1-benzopyran-4-one:



In contrast to the disclosure of Gammill, the compounds of the invention are defined by the structure shown below.



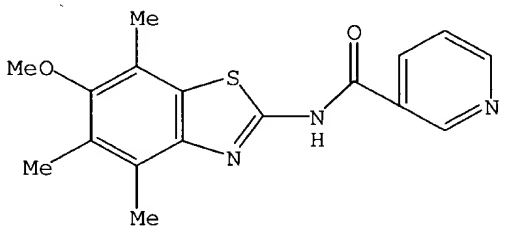
(III)

Claims 1-4, 28, 29, 32 and 48 have been canceled. According to Gammill, the portion of the molecule corresponding to R_2 taken together with R_3 is 2-morpholine-pyran-4-one. In contrast, the compounds of the invention can have R_2 and R_3 taken together to form a heterocycle, but not optionally substituted pyran-4-one (*see, e.g.*, claims 33, 42 and 46). Therefore, Gammill does not anticipate claims 42-47, 53, 54, 56 and 57. Applicants respectfully submit that the rejection has been overcome and should be withdrawn.

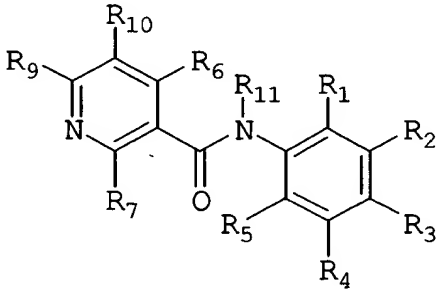
D. Fourth rejection (Claims 1-4, 28, 29, 32, 53 and 55-57)

Claims 1-4, 28, 29, 32, 53 and 55-57 were rejected under 35 U.S.C. § 102(b) as being anticipated by Okamoto ('519) patent. (Office Action, page 15, lines 7-8). Applicants respectfully traverse this rejection. The Examiner states "Compound 8 anticipated Applicants' use claims and fits formula (V) with Ar' = 3-pyridyl and Ar = 6-methoxy-4,5,7-trimethylbenzothiaz-2-yl. The compound is found in Example 8, lines 31-55, column 21. Activity against psoriasis is taugh in line 38, column 17. Activity against inflammatory bowel disease is claimed in claim 17." (Office Action, page 15, lines 8-12). Applicants respectfully disagree.

Okamoto discloses the compound, 6-methoxy-4,5,7-trimethylbenzothiaz-2-yl-3-pyridinecarboxamide:



In contrast to Okamoto, the compounds of the present invention are defined by the structure shown below.



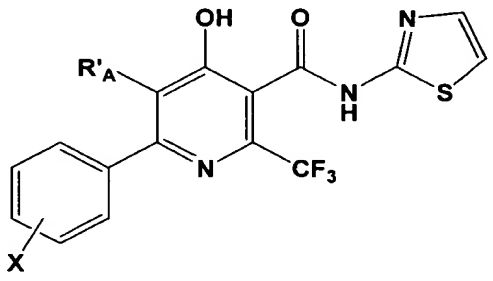
(III)

Claims 1-4, 28, 29 and 32 have been canceled. The compounds of Okamoto have a substituted benzothiaz-2-yl group bonded to the 3-pyridinecarboxamide portion of the molecule. In contrast to the disclosure of Okamoto, the compounds of the present invention have an optionally substituted phenyl group bonded to the 3-pyridinecarboxamide portion. Okamoto, therefore, does not anticipate claims 53 and 55-57. Applicants respectfully submit that the rejection has been overcome and should be withdrawn.

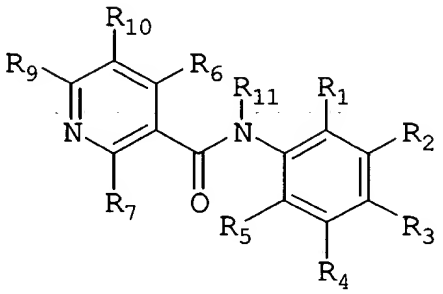
E. Fifth rejection (Claims 1-4, 28, 29, 32, 53 and 55-57)

Claims 1-4, 28, 29, 32, 53 and 55-57 were rejected under 35 U.S.C. § 102(b) as being anticipated by Clémence (FR 2,636,329 A2). (Office Action, page 15, lines 13-14). Applicants respectfully traverse this rejection. The Examiner is of the opinion that "[o]ne compound of this reference anticipated Applicants' use claims and fit formula (V) with Ar' = substituted 3-pyridyl and Ar = thiaz-2-yl. Activity against psoriasis is taught in line 38, column 17. Activity against autoimmune diseases and rheumatoid arthritis is taught in lines 22-25, page 8." (Office Action, page 15, lines 14-18). Applicants respectfully disagree.

Clémence discloses, generally, compounds of the formula:



In contrast to Clémence, the compounds of the present invention are defined by the structure shown below.



(III)

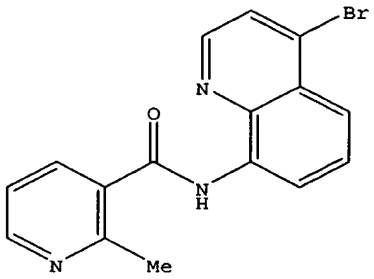
Claims 1-4, 28, 29 and 32 have been canceled. Clémence discloses, generally, pyridine carboxamides having a thiaz-2-yl group bonded to the 3-pyridinecarboxamide portion of the molecule. In contrast to the disclosure of Clémence, the compounds of the present invention have an optionally substituted phenyl group bonded to the 3-pyridinecarboxamide portion. Clémence, therefore, does not anticipate claims 53 and 55-57. Applicants respectfully submit that the rejection has been overcome and should be withdrawn.

F. Sixth rejection (Claims 1-4, 28, 29, 32, 53 and 54)

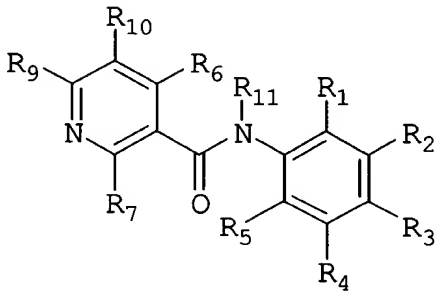
Claims 1-4, 28, 29, 32, 53 and 54 were rejected under 35 U.S.C. § 102(a) as being anticipated by Oku (JP 10291988 A2). (Office Action, page 16, lines 1-2). Applicants respectfully traverse this rejection. The Examiner is of the opinion that "[t]here are sixty compounds of this reference which anticipated Applicants' use claims and fit formula (V) with Ar' = substituted 3-pyridyl and Ar = substituted quinolyl[.] Activity against rheumatoid

arthritis is taught in the abstract." (Office Action, page 16, lines 2-5). Applicants respectfully disagree.

Oku discloses, for example, compounds of the formula:



In contrast to Oku, the compounds of the present invention are defined by the structure shown below.



(III)

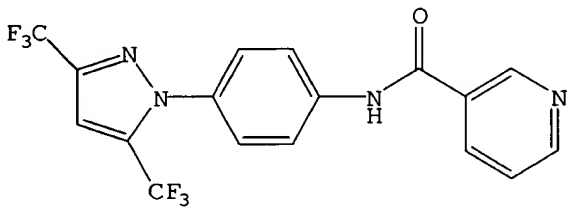
Claims 1-4, 28, 29 and 32 have been canceled. In all of the relevant compounds disclosed in Oku, the portion of the molecule corresponding to R_1 taken together with R_2 is optionally substituted pyrido. In contrast, the compounds of the present invention cannot have R_1 and R_2 taken together to form pyrido. (*see, e.g.*, claims 33-35). Claims 33-35 only include fused heterocycle, not fused heteroaryl. Heterocylce, as used herein, is defined in the specification on page 20, lines 18-25, and includes only saturated or partially saturated heterocycles, which does not include the group pyrido, as described in Oku. Therefore, Oku

does not anticipate claims 53 and 54. Applicants respectfully submit that the rejection has been overcome and should be withdrawn.

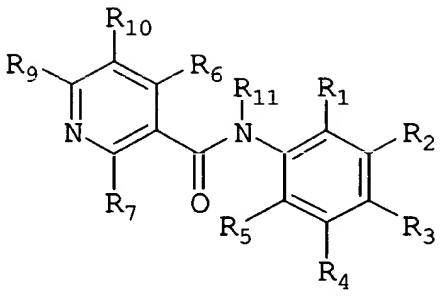
G. Seventh rejection (Claims 1-4, 28, 29, 32, 33, 36, 38, 53-54)

Claims 1-4, 28, 29, 32, 33, 36, 38, 53-54 have been rejected 35 U.S.C. § 102(a) as being anticipated by Kubotab (WO 9919303 A1). (Office Action, page 16, lines 7-8). Applicants respectfully traverse this rejection. The examiner is of the opinion that "[t]here is one compound in this reference, which anticipates Applicants' use claims. The compound is shown below and fits formula (V) with Ar' = 3-pyridyl and Ar = 4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl with R_3 = 3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl. Activity against autoimmune diseases and rheumatoid arthritis is taught in the abstract." (Office Action, page 16, lines 8-13). Applicants respectfully disagree.

Kubotab discloses 4-[3,5-(bistrifluoromethyl)-1H-pyrazol-1-yl]-phenyl-3-pyridinecarboxamide:



In contrast to Kubotab, the compounds disclosed in the present invention are defined by the structure shown below.



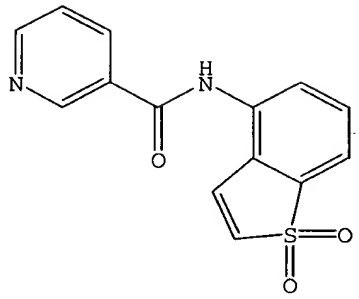
(III)

Claims 1-4, 28, 29 and 32 have been canceled. The compounds of Kubotab have a 1H-pyrazolyl group corresponding to the group R_3 in the present invention. In contrast to the disclosure of Kubotab, compounds of the present invention cannot have optionally substituted pyrazolyl as R_3 when R_{1-2} and R_{4-11} are hydrogen. Kubotab, therefore, does not anticipate claims 33, 36, 38 and 53-54. Applicants respectfully submit that the rejection has been overcome and should be withdrawn.

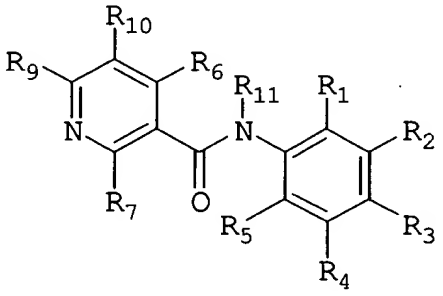
H. Eighth rejection (Claims 1-4, 28, 29, 32-36, 42-48, 53, 54, 56 and 57)

Claims 1-4, 28, 29, 32-36, 42-48, 53, 54, 56 and 57 have been rejected under 35 U.S.C. § 102(a) as being anticipated by Konishi (WO 9951587 A1). (Office Action, page 17, lines 1-2). Applicants respectfully traverse this rejection. The Examiner is of the opinion that "[t]here are five compounds in the reference, which anticipate Applicants' use claims including the one shown below. The compound is shown below and fits formula (V) with Ar' = 3-pyridyl and Ar = 1,1-dioxidobenzo[b]thien-4-yl, with $R_1 = R_2$ = thienyl. Activity against multiple myeloma, plasma cell leukemia, psoriasis, renal cell cancer, chronic rheumatoid arthritis, and autoimmune diseases, is taught in the abstract." (Office Action, page 17, lines 2-7). Applicants respectfully disagree.

Konishi discloses, for example, 3-pyridinecarboxamide, N-(1,1-dioxidobenzo[b]thien-4-yl):



In contrast to Konishi, the compounds disclosed in the present invention are defined by the structure shown below.



(III)

Claims 1-4, 28, 29, 32 and 48 have been canceled. According to Konishi, the portion of the molecule corresponding to R_5 taken together with R_4 is the unsaturated group thienyl-1,1-dioxide or the partially saturated thienyl-1,1-dioxide. In contrast, the compounds of the present invention cannot have R_1 and R_2 that can be taken together to form the unsaturated heterocycle thienyl-1,1-dioxide (*see*, *e.g.*, claims 33-35). Claims 33-35 only include fused heterocycle, not fused heteroaryl. Heterocycle, as used herein, is defined in the specification on page 20, lines 18-25, and includes only saturated or partially saturated heterocycles, which does not include the unsaturated group thienyl-1,1-dioxide, as described in Konishi. Further,

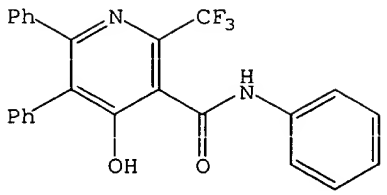
claims 33-35 do not include the group optionally substituted partially saturated thienyl-1,1-dioxide.

Additionally, Konishi discloses three additional compounds with substituted alkyl groups in the position corresponding to R_4 in the compounds of the present invention. In contrast to Konishi, the compounds of the present invention cannot have R_4 be optionally substituted alkyl when R_{1-3} and R_{5-11} are hydrogen (*e.g.*, see claim 33, 34, 42 and 46). Therefore, Konishi does not anticipate claims 33-36, 42-48, 53, 54, 56 and 57. Applicants respectfully submit that the rejection has been overcome and should be withdrawn.

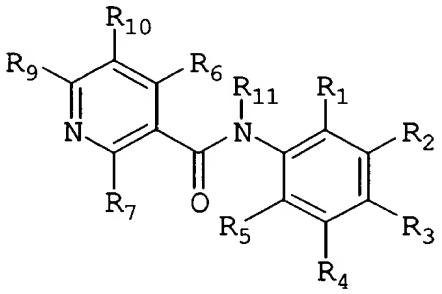
I. Ninth rejection (Claims 1-4, 28, 29, 32, 33, 53 and 54)

Claims 1-4, 28, 29, 32, 33, 53 and 54 were rejected under 35 U.S.C. § 102(b) as being anticipated by Clemence ('140 patent). (Office Action, page 17, lines 11-12). Applicants respectfully traverse this rejection. The Examiner is of the opinion that "[t]here is one compound in this reference, which anticipates Applicant's use claims. The compound is shown below and fits formula (V) with Ar' = 4-hydroxy-5,6-diphenyl-2-(trifluoromethyl)-3-pyridyl, with R_6 = hydroxy, R_7 = trifluoromethyl, $R_9 = R_{10}$ = phenyl and Ar = phenyl. It is Example 4, lines 13, column 10 to line 43, column 11. Activity against rheumatoid arthritis is taught in the claim 15 of the reference." (Office Action, page 17, line 12 through page 18, line 2). Applicants respectfully disagree.

Clémence discloses the compound 4-hydroxy-5,6-diphenyl-2-trifluoromethyl-N-phenyl-3-pyridinecarboximide:



In contrast to Clémence, compounds of the present invention are represented by Formula III:



(III)

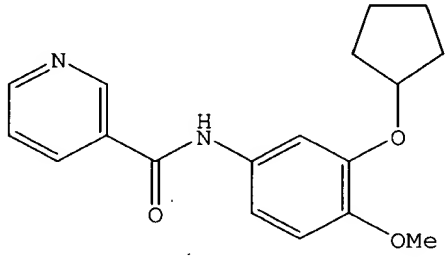
Claims 1-4, 28, 29 and 32 have been canceled. The compounds of the invention, as defined by Formula (III), do not include compounds wherein both R_9 and R_{10} are phenyl and $R_{1\text{-}5}$ are hydrogen. Therefore, Clemence does not anticipate claims 33, 53 and 54. Applicants respectfully submit the rejection has been overcome and should be withdrawn.

J. Tenth rejection (Claims 1-4, 28, 29, 32, 33, 36, 56 and 57)

Claims 1-4, 28, 29, 32, 33, 36, 56 and 57 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Beeley ('827 patent). (Office Action, page 18, lines 4-5). Applicants respectfully traverse this rejection. The Examiner is of the opinion that "[t]here is one compound in this reference, which anticipates Applicant's use claims. The compound is shown below and fits formula (V) with Ar' = 3-pyridyl and Ar = 3-(cyclopentyloxy)-4-

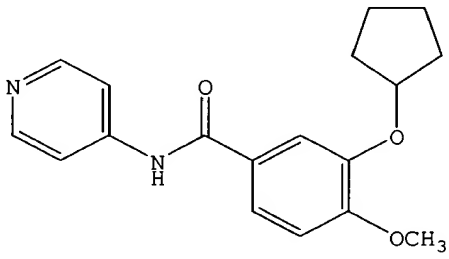
methoxyphenyl with R_3 = methoxy and R_4 = cyclopentyloxy. It is Example 7, lines 11-19, column 10. Activity against psoriasis is taught in line 32, column 5." (Office Action, page 18, lines 5-9). Applicants respectfully disagree.

The Examiner is of the opinion that the structure of Compound 16, disclosed in Beeley, is the following:

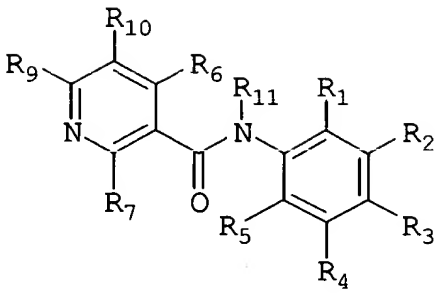


(Office Action, page 18, line 10).

Applicants respectfully submit that the Examiner misapprehended the chemical structure of Compound 16, disclosed in Beeley, which is in fact N-pyridin-4-yl-3-cyclopentyloxy-4-methoxybenzamide:



In contrast to Beeley, compounds of the present invention are represented by Formula III:



(III)

Claims 1-4, 28, 29 and 32 have been canceled. The compounds of Beeley are N-pyridin-4-yl carboxamides. In contrast to the disclosure of Beeley, compounds of the present invention are not N-pyridin-4-yl carboxamides but optionally substituted 3-pyridyl-N-phenyl carboxamides. Beeley, therefore, does not anticipate claims 33, 36, 56 and 57. Applicants respectfully submit that the rejection has been overcome and should be withdrawn.

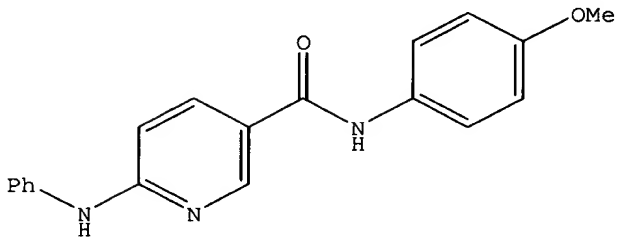
K. Eleventh rejection (Claims 1-4, 28, 29, 32, 33, 36, 42-48 and 53-57)

Claims 1-4, 28, 29, 32, 33, 36, 42-48 and 53-57 were rejected under 35 U.S.C. § 102(e) as being anticipated by Mantlo ('884 patent). (Office Action, page 18, lines 11-12). Applicants respectfully traverse this rejection. Specifically, the Examiner is of the opinion that:

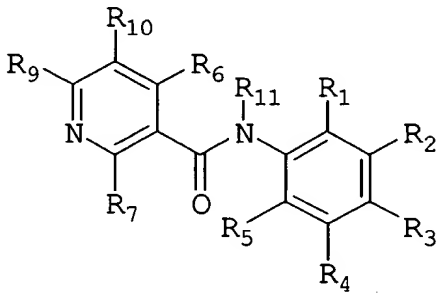
> There are over one hundred compounds disclosed in this reference, which anticipate Applicant's use claims. One compound is shown below and fits formula (V) with Ar' = (6-phenylamino)-3-pyridyl with R_9 = phenylamino and Ar = 4-methoxyphenyl with R_3 = methoxy. The compounds are found in Tables 8-13, spanning columns 84-91. See also compound claims 1-15 in this reference. Activity against rheumatoid arthritis is taught in line 36, column 96 of the reference. Activity against inflammatory bowel disease and psoriasis is taught in line 40-41, column 96. Activity against cancer is taught in line 57, column 96.

(Office Action, page 18, line 12, through page 17, line 4). Applicants respectfully disagree.

Mantlo discloses, for example, 6-(phenylamino)-N-(4-methoxyphenyl)-3-pyridinecarboxamide:



In contrast to Mantlo, compounds of the present invention are represented by Formula III:



(III)

Claims 1-4, 28, 29, 32, 44 and 48 have been canceled. All the relevant compounds disclosed in Mantlo have an N-substituted amino group corresponding to the group R_9 in the present invention. The relevant compounds in Mantlo are N-substituted by aryl or cycloalkyl groups. In contrast to the disclosure of Mantlo, the compounds of the present invention cannot have R_9 be amino substituted by aryl or cycloalkyl groups. Mantlo, therefore, does not anticipate claims 33, 36, 42-47 and 53-57. Applicants respectfully submit that the rejection has been overcome and should be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

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Registration No. 32,893

Date: July 11, 2002

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Version with markings to show changes made

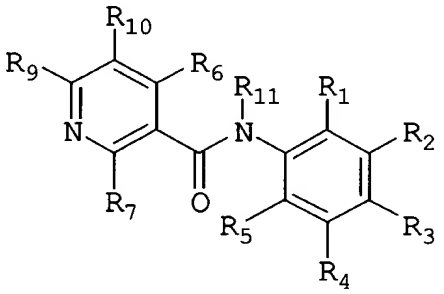
In the Claims:

Claims 1-32, 44, 48, and 62-70 were canceled without prejudice or disclaimer to the subject matter thereof.

Claims 72-75 were added.

Claims 33, 34, 35, 42, 43, 46, 47, 53, 54, 55, 56, 58 and 71 were amended as follows:

33. (Once Amended) [The method of claim 32, wherein said compound is of Formula III:] A method of treating a disorder responsive to the induction of apoptosis in an animal suffering therefrom, comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula III:



(III)

or a pharmaceutically acceptable salt or prodrug thereof, wherein

R_1-R_7 and R_9-R_{10} are independently hydrogen, halo, haloalkyl, haloalkoxy, aryl, fused aryl, carbocyclic, fused carbocyclic, a heterocyclic group, fused heterocyclic, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, nitro, [amino,] aminoalkyl, cyano, cyanoalkyl, acyl, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, alkoxycarbonyl, aryloxy, arylalkoxy, carboxy, carbonylamido or alkylthiol[; and], $-NH_2$, $-NHR_{15}$ or $-NR_{15}R_{16}$, wherein

R_{15} and R_{16} are independently optionally substituted C_{1-10} alkyl, heterocyclic or heteroaryl groups; and

R_{11} is hydrogen; or alkyl, cycloalkyl, aryl or heteroaryl, each of which is optionally substituted;

provided that:

when R_{1-2} and R_{4-11} are hydrogen, R_3 is not optionally substituted pyrazolyl;

when R_{1-5} are hydrogen, each of R_9 and R_{10} are not phenyl;

when R_3 is methoxy and R_{5-11} are hydrogen, each of R_2 and R_4 are not cyclopentyloxy;

when R_{1-3} and R_{5-11} are hydrogen, R_4 is not optionally substituted alkyl;

when R_{3-11} are hydrogen, R_1 and R_2 are not taken together to form optionally substituted thienyl-1,1-dioxide or partially saturated thienyl-1,1-dioxide; and

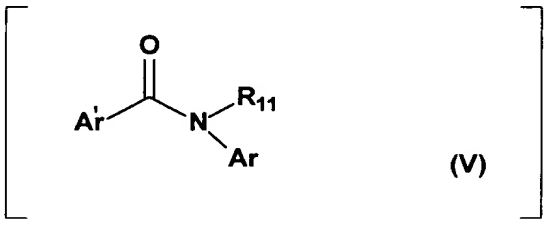
when R_1 and R_{4-11} are hydrogen, R_2 and R_3 are not taken together to form substituted pyranyl.

34. (Once Amended) The method of claim 33, wherein R_1 and R_2, or R_2 and R_3, or R_3 and R_4, or R_4 and R_5 are taken together to form an optionally substituted carbocycle or an optionally substituted heterocycle, provided that said optionally substituted heterocycle is not optionally substituted saturated or partially saturated thienyl-1,1-dioxide or substituted pyranyl.

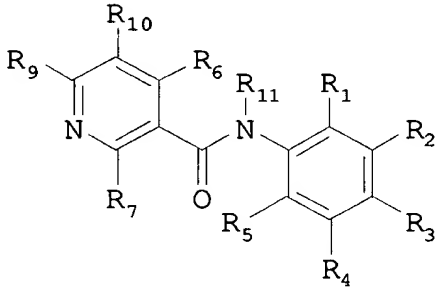
35. (Once Amended) The method of claim 34, wherein said R_1 and R_2, or R_2 and R_3, or R_3 and R_4, or R_4 and R_5 are taken together to form $-OCH_2O-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-OCH_2CH_2O-$, $-CH_2N(R)CH_2-$, $-CH_2CH_2N(R)CH_2-$, $-CH_2N(R)CH_2CH_2-$, $-CH=CH-CH=CH-$, $-N(R)-CH=CH-$, $-CH=CH-N(R)-$, $-O-CH=CH-$, $-CH=CH-O-$, [$-S-CH=CH-$, $-CH=CH-S-$, $-N=CH-CH=CH-$, $-CH=N-CH=CH-$, $-CH=CH-N=CH-$, $-CH=CH-CH=N-$] or $-N=CH-CH=N-$, wherein the carbocycle or heterocycle is optionally substituted, and R is hydrogen, alkyl, haloalkyl, aryl, fused aryl, carbocyclic, a heterocyclic group, a heteroaryl group, alkenyl,

alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl or aminoalkyl.

42. (Once Amended) A method for treating [or preventing] cancer, comprising administering to an animal in need of such treatment an effective amount of a compound of Formula [V] III:



(V)



(III)

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

[Ar' and Ar are independently optionally substituted aryl or optionally substituted heteroaryl, provided that the ring structure of said optionally substituted heteroaryl comprises not more than two nitrogen atoms; and]

R_1-R_7 and R_9-R_{10} are independently hydrogen, halo, haloalkyl, haloalkoxy, aryl, fused aryl, carbocyclic, fused carbocyclic, a heterocyclic group, fused heterocyclic, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, nitro, [amino,] aminoalkyl, cyano, cyanoalkyl, acyl, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, alkoxycarbonyl, aryloxy, arylalkoxy, carboxy, carbonylamido or alkylthiol[; and], $-NH_2$, $-NHR_{15}$ or $-NR_{15}R_{16}$, wherein

R_{15} and R_{16} are independently optionally substituted C_{1-10} alkyl, heterocyclic or heteroaryl groups; and

R_{11} is hydrogen; or alkyl, cycloalkyl, aryl or heteroaryl, each of which is optionally substituted;

provided that:

when R_{1-2} and R_{4-11} are hydrogen, R_3 is not optionally substituted pyrazolyl;

when R_{1-5} are hydrogen, each of R_9 and R_{10} are not phenyl;

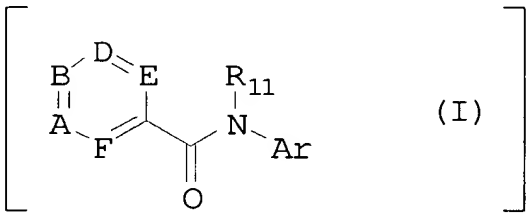
when R_3 is methoxy and R_{5-11} are hydrogen, each of R_2 and R_4 are not cyclopentyloxy;

when R_{1-3} and R_{5-11} are hydrogen, R_4 is not alkyl;

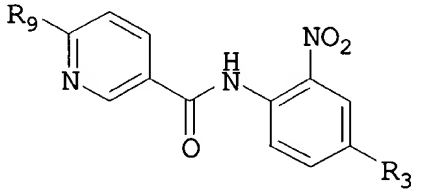
when R_{3-11} are hydrogen, R_1 and R_2 are not taken together to form optionally substituted thienyl-1,1-dioxide or partially saturated thienyl-1,1-dioxide; and

when R_1 and R_{4-11} are hydrogen, R_2 and R_3 are not taken together to form substituted pyranyl.

43. (Once Amended) The method of claim 42, wherein said compound is of Formula [I] IV:



(I)



(IV)

or pharmaceutically acceptable salts or prodrugs thereof[, wherein:

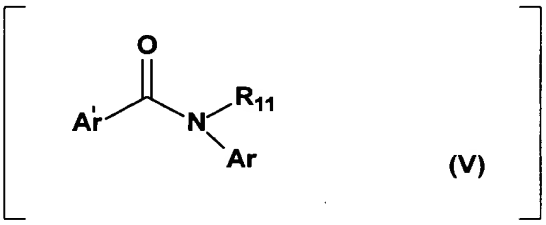
A is N or C-R_8, B is N or C-R_9, D is N or C-R_{10}, E is N or C-R_6 and F is N or C-R_7, provided that not more than two of A, B, D, E and F are N in the same time;

Ar is optionally substituted and is an aryl or heteroaryl;

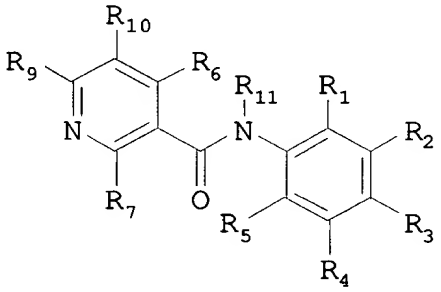
R_6-R_{10} are independently hydrogen, halo, haloalkyl, aryl, fused aryl, carbocyclic, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido or alkylthiol; and

R_{11} is hydrogen or optionally substituted alkyl, cycloalkyl, aryl, or heteroaryl].

46. (Once Amended) A method for the treatment of drug resistant cancer, comprising administering to an animal in need of such treatment an effective amount of a compound of the Formula [V] III:



(V)



(III)

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

[Ar' and Ar are independently optionally substituted aryl or optionally substituted heteroaryl, provided that the ring structure of said optionally substituted heteroaryl comprises not more than two nitrogen atoms; and]

R_1-R_7 and R_9-R_{10} are independently hydrogen, halo, haloalkyl, haloalkoxy, aryl, fused aryl, carbocyclic, fused carbocyclic, a heterocyclic group, fused heterocyclic, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl,

heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, nitro, [amino,] aminoalkyl, cyano, cyanoalkyl, acyl, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, alkoxycarbonyl, aryloxy, arylalkoxy, carboxy, carbonylamido or alkylthiol[; and], $-NH_2$, $-NHR_{15}$ or $-NR_{15}R_{16}$, wherein

R_{15} and R_{16} are independently optionally substituted C_{1-10} alkyl, heterocyclic or heteroaryl groups; and

R_{11} is hydrogen; or alkyl, cycloalkyl, aryl or heteroaryl, each of which is optionally substituted;

provided that:

when R_{1-2} and R_{4-11} are hydrogen, R_3 is not optionally substituted pyrazolyl;

when R_{1-5} are hydrogen, each of R_9 and R_{10} are not phenyl;

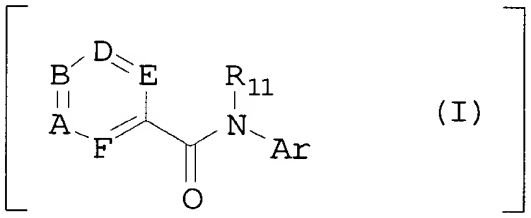
when R_3 is methoxy and R_{5-11} are hydrogen, each of R_2 and R_4 are not cyclopentyloxy;

when R_{1-3} and R_{5-11} are hydrogen, R_4 is not alkyl;

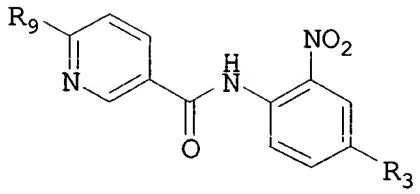
when R_{3-11} are hydrogen, R_1 and R_2 are not taken together to form optionally substituted thienyl-1,1-dioxide or partially saturated thienyl-1,1-dioxide; and

when R_1 and R_{4-11} are hydrogen, R_2 and R_3 are not taken together to form substituted pyranyl.

47. (Once Amended) The method of claim 46, wherein said compound is of Formula [I] IV:



(I)



(IV)

or pharmaceutically acceptable salts or prodrugs thereof [, wherein:

A is N or C-R_8, B is N or C-R_9, D is N or C-R_{10}, E is N or C-R_6 and F is N or C-R_7, provided that not more than two of A, B, D, E and F are N in the same time;

Ar is optionally substituted and is an aryl or heteroaryl;

R_6-R_{10} are independently hydrogen, halo, haloalkyl, aryl, fused aryl, carbocyclic, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido or alkylthiol; and

R_{11} is hydrogen or optionally substituted alkyl, cycloalkyl, aryl, or heteroaryl].

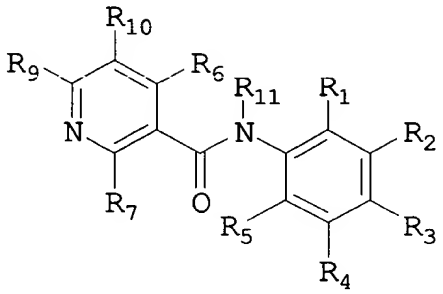
53. (Once Amended) The method of claim [1] 33, wherein said disorder is an autoimmune disease.

54. (Once Amended) The method of claim [1] 33, wherein said disorder is rheumatoid arthritis.

55. (Once Amended) The method of claim [1] 33, wherein said disorder is inflammatory bowel disease.

56. (Once Amended) The method of claim [1] 33, wherein said disorder is a skin disease.

58. (Once Amended) A compound of Formula III:



(III)

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R_1 and R_5 are independently selected from the group consisting of hydrogen, hydroxy, alkyl, alkoxy, halogen, NO_2, cyano, haloalkyl, haloalkoxy, amino and aminoalkyl, provided that at least one of R_1 and R_5 is selected from the group consisting of NO_2, cyano, alkyl and haloalkyl;

R_2 and R_4 are independently selected from the group consisting of hydrogen, hydroxy, halogen, cyano, haloalkyl, haloalkoxy, amino and aminoalkyl;

R_3 is alkyl, Cl, F, haloalkyl, alkoxy, arylalkoxy, cyano, haloalkyloxy, amino or aminoalkyl;

R_6 is hydrogen, hydroxy, alkyl, NO_2, cyano, haloalkyl, haloalkyloxy, amino or aminoalkyl;

R_7 is hydrogen, hydroxy, alkyl, NO_2, cyano, haloalkyl, haloalkyloxy, amino or aminoalkyl;

R_9 is hydroxy, alkyl, halogen, NO_2, haloalkyl, alkoxy, cyano, haloalkyloxy, amino or aminoalkyl;

R_{10} is hydrogen, hydroxy, alkyl, Cl, F, NO_2, cyano, haloalkyl, haloalkyloxy, amino or aminoalkyl; and

R_{11} is hydrogen, alkyl or haloalkyl;

provided that when R_2 and R_4 are hydrogen and $R_{9\text{-}10}$ are halo, R_1 or R_5 and R_3 are not both alkyl.

71. (Once Amended) A pharmaceutical composition, comprising the compound of any one of claims 58-[70]61, and a pharmaceutically acceptable carrier.

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